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A FURTHER ANALYSIS OF THE HEREDITARY TRANSMISSION OF DEGENERACY AND DEFORMITIES BY THE DESCENDANTS OF ALCOHOLIZED MAMMALS. II

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The Influence of Internal and External Factors on the Quality of the Offspring

Table II gives the relationship between the size of the litters and the mortality of the descendants from different combinations. It brings out in a way the variable internal and external factors to be considered in interpreting the conditions of the members of the numerous litters of animals. The external factor considered in the table is one of nutrition or environment, depending upon the number of young developed in the uterus at any one time. The table indicates the influence of an internal factor, the germ plasms concerned in mating related or non-related animals. Four combinations are considered: pairs of normal non-relatives, pairs of alcoholic non-relatives, pairs of normal relatives, and pairs of alcoholic relatives.

The first vertical column shows that in mating together normal non-related guinea pigs of the stocks used in these experiments the average litter contains 1.96 individuals. Fifty-one and eleven hundredths per cent. of the young were found in litters of two, and 20 per cent. of the animals occurred in litters of three. Fifteen and fifty-five hundredths per cent. of the animals were born in litters of only one young, and 13.33 per cent. in litters of four individuals.

The next space below in the table shows the number and percentage of individuals living over three months

TABLE II

THE SIZE OF LITTERS AND MORTALITY OF DESCENDANTS FROM DIFFERENT COMBINATIONS

	Normal Lines 90				Alcoholic Lines 401				Normal Inbred 30				Alcoholic Inbred 135			
Total number.	1 in litt. 14 (15.55%)	2 in litt. 46 (51.11%)	3 in litt. 18 (20%)	4 in litt. 12 (13.33%)	1 in litt. 84 (20.94%)	2 in litt. 214 (53.36%)	3 in litt. 87 (21.69%)	4 in litt. 16 (3.99%)	1 in litt. 12 (40%)	2 in litt. 18 (60%)	3 in litt. 0	4 in litt. 0	1 in litt. 38 (28.14%)	2 in litt. 76 (56.29%)	3 in litt. 21 (15.55%)	4 in litt. 0
	(Average number of young per litter 1.96)				(Average number of young per litter 1.79)				(Average number of young per litter 1.43)				(Average number of young per litter 1.62)			
Lived over 3 months....	1 in litt. 12 (85.71%)	2 in litt. 40 (86.95%)	3 in litt. 11 (61.11%)	4 in litt. 4 (33.33%)	1 in litt. 54 (64.28%)	2 in litt. 109 (50.93%)	3 in litt. 19 (21.83%)	4 in litt. 3 (18.75%)	1 in litt. 12 (100%)	2 in litt. 12 (66.66%)	3 in litt. 0	4 in litt. 0	1 in litt. 29 (76.31%)	2 in litt. 20 (26.31%)	3 in litt. 0	4 in litt. 0
	(All together 74.44%)				(All together 46.13%)				(All together 80%)				(All together 36.29%)			
Died within 3 months	1 in litt. 2 (14.28%)	2 in litt. 6 (13.04%)	3 in litt. 7 (38.88%)	4 in litt. 8 (66.66%)	1 in litt. 30 (35.71%)	2 in litt. 105 (49.06%)	3 in litt. 68 (78.16%)	4 in litt. 13 (81.24%	1 in litt. 0	2 in litt. 6 (33.33%)	3 in litt. 0	4 in litt. 0	1 in litt. 9 (23.68%)	2 in litt. 56 (73.68%)	3 in litt. 21 (100%)	4 in litt. 0
	(All together 25.56%)				(All together 53.86%)				(All together 20%)				(All together 63.70%)			
Deformed....	1 in litt. 0	2 in litt. 0	3 in litt. 0	4 in litt. 0	1 in litt. 2 (2.25%)	2 in litt. 9 (4.20%)	3 in litt. 10 (11.49%)	4 in litt. 0	1 in litt. 0	2 in litt. 0	3 in litt. 0	4 in litt. 0	1 in litt. 2 (5.26%)	2 in litt. 14 (18.42%)	3 in litt. 4 (19.04%)	4 in litt. 0
					(All together 5.23%)								(All together 14.81%)			
Undersize (less than $\frac{2}{3}$ of the average weight)....	1 in litt. 0	2 in litt. 0	3 in litt. 0	4 in litt. 0	1 in litt. 1 (1.19%)	2 in litt. 4 (1.86%)	3 in litt. 3 (3.44%)	4 in litt. 2 (12.50%)	1 in litt. 0	2 in litt. 1 (5.55%)	3 in litt. 0	4 in litt. 0	1 in litt. 1 (2.89%)	2 in litt. 4 (5.26%)	3 in litt. 0	4 in litt. 0
					(All together 2.49%)				(All together 3.33%)				(All together 3.70%)			

in the different-size litters. Almost 86 per cent. of the individuals born one in a litter lived, and about 87 per cent., 40 out of 46, of those born two in a litter lived. When there were three in a litter, however, only 61 per cent. lived and of those born four in a litter, it happened that only one third of them survived, though there were only a few in all. Of the total number of young from normal non-related parents 74.44 per cent. lived. Judging from these statistics litters of one or two young are the most vigorous and individuals born in litters of three or four are not so likely to be strong and long-lived.

The next space below gives the mortality records, which, of course, is merely another way of bringing out the above statements. The space following contains the number of deformed animals, but from the normal matings not one such individual has been produced. The last space gives the number of small-size or dwarf specimens also, none of which occur among these litters from normal non-related parents.

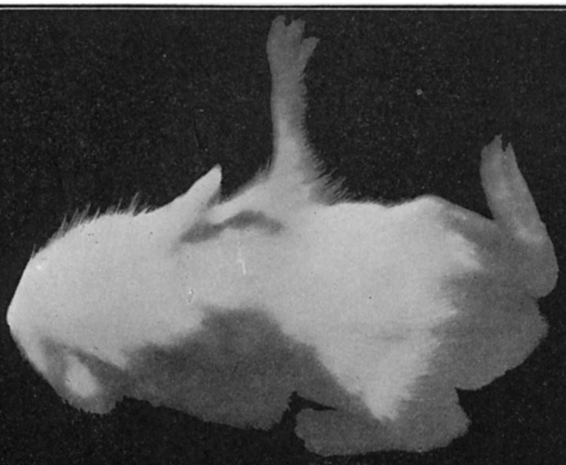
The second vertical column contains a similar analysis of the influence of the size of the litter on the mortality and condition of the young born from non-related alcoholic parentage. This not only includes the offspring from directly treated animals, but also other matings of non-relatives belonging to the alcoholic lines. Here again the majority of all the young, 53.36 per cent., are born in litters of two. Litters containing three are next in frequency, followed by litters of only a single individual. Of the total number of offspring produced by alcoholic parents 21.69 per cent. occurred in litters of three, and only about 4 per cent. of the offspring were members of litters of four individuals. The average number of young in the litters from these animals is 1.79, somewhat smaller than from normal matings.

The space below shows that in all only 46.13 per cent. of these young survived, whereas more than half as many more, or 74.44 per cent., from normal parentage lived over three months. The most vigorous animals are those born only one in a litter. Sixty-four and twenty-eight hundredths per cent. of them lived. While about 51 per cent. of the two-in-a-litter individuals survived, only about 22 per cent. of the young born three in a litter were capable of surviving, and only 18.75 per cent. of the individuals from the litters of four lived more than three months. These figures indicate that the offspring from similarly injured parents are more capable of survival when born in a small litter of one or two than when contained in larger litters of three or four.

This is not on account of the fact that the treated or degenerate mother is more incapable of nourishing the larger litters, since the same is true of the larger litters from normal mothers, as shown by the previous column. The fact is that all young of large litters tend to be small and weak at birth, whereas a single young is far better accommodated. For these reasons it is always of importance to know the size of the litter in which an animal was born in estimating the degenerate qualities it may possess as compared with the qualities of another individual. For example, one animal may appear larger and stronger than another, and yet when bred will give rise to more degenerate offspring than the weaker individual. Although having a vigorous body, its germ-cell complex was not so good as that of the weaker animal, from a larger litter which produces better offspring. Therefore, the small weak males bred to normal females do not always give the poorer results when compared with the matings of stronger males and normal females.

The next space is the reverse of the one above and shows the percentages of mortality among the offspring derived from alcoholic non-relatives. More than half of the young, 53.86 per cent., from these combinations die soon after birth, a mortality record just twice as high as that of the control animals.

The next space shows the frequency of deformities among such young. Here it is again clearly indicated that the animals born one in a litter are better than those



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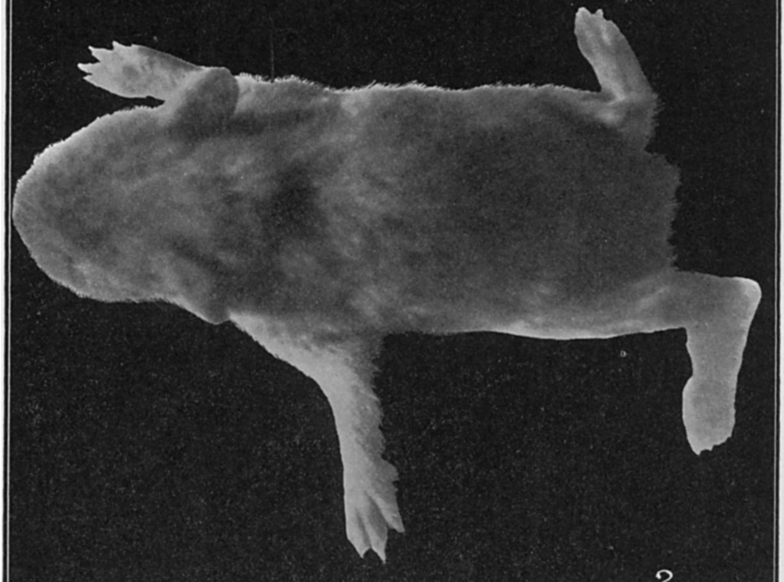

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FIG. 1. 521 albino F_2 ♀ (two alcoholic grandmothers, both grandfathers normal). Lived only one day after birth; the meninges of the brain were filled with blood. Gross tremor and complete paralysis of right side. Cataracts, both crystalline lenses being entirely opaque. The photograph shows the outstretched paralyzed right extremities while the left legs are held in a normal position in their effort to support the body. (Birth weight, 54 grams.)

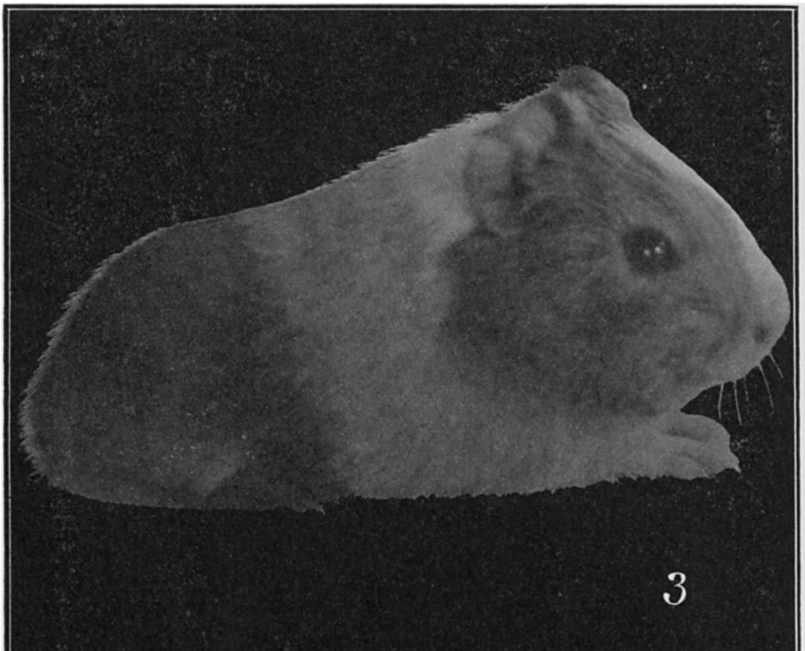
FIG. 2. 506 mouse and yellow $F_{2,3}$ ♂ (two paternal great-grandmothers and the maternal grandmother alcoholic, slightly inbred). Gross tremor and complete paralysis of left side so unable to walk. Cornea of right eye opaque. Photograph shows the powerless condition of the outstretched left legs with the right legs attempting to support the body. (Birth weight, 57 grams.) The two figures are at different magnifications.

from litters of two, which are in turn better than the members of the litters of three individuals. Only 2.25 per cent. of the 84 individuals born in litters of one were deformed. While 9 of the 214 individuals born two in a litter, or 4.2 per cent., almost twice as many, were deformed. And 10 of the 87 animals born three in a litter were deformed, or about 11.5 per cent., which is almost five times higher than the number of deformities found among the animals born in litters of single individuals. Among the descendants of alcoholic non-relatives there was in all 5.23 per cent. of deformed specimens, whereas not one deformed animal arose from similar normal matings.

The last space of this column indicates the number of dwarf or undersize animals produced in the different litters from non-related alcoholic lines. Among the 84 animals born one in a litter only a single individual was of unusually small size. The 214 animals born in litters of two were all of average size except four, or stated exactly, 1.86 per cent. of them were undersize. In the litters of three 3.44 per cent. of the animals were small, while 12.5 per cent. of the members of litters of four were small specimens. Here again it is shown that the members of large litters are not so uniformly up to the standard of size and vigor as animals born in litters of only one or two individuals.

The third vertical column gives a similar analysis of the few normal inbred individuals which have been produced during the time of the experiment. There are not many such matings, as a general effort has been made to avoid inbreeding the control animals since this might be considered to vitiate the results.

The few young produced by inbred normal matings have all been in litters of only one or two offspring, so that the size of the litters averages only 1.43 individuals. The size of the litters is, therefore, smaller than from either the non-related normal or alcoholic animals. Eighty per cent. of the young have survived, more, however, from the



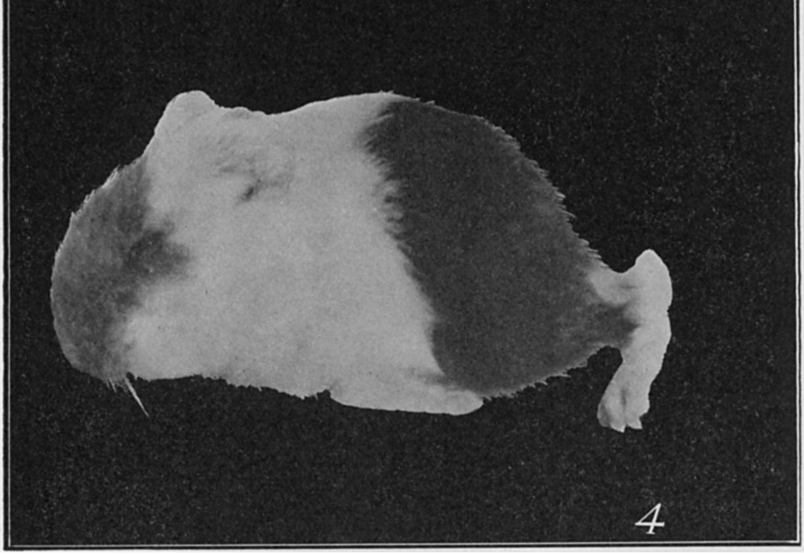


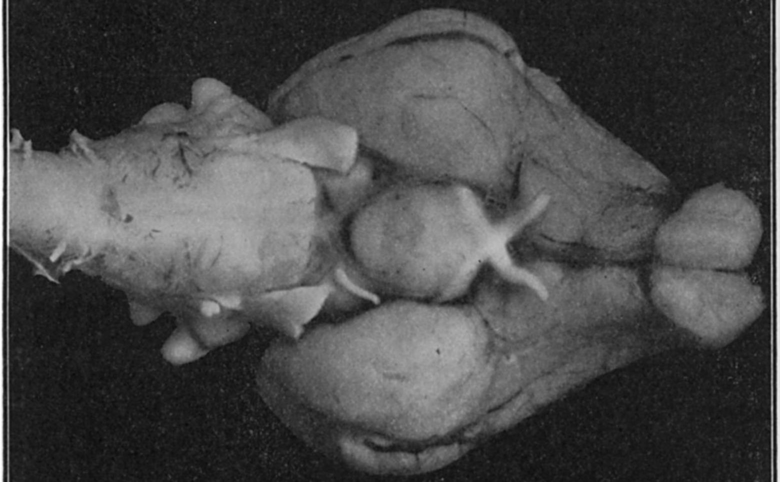
FIG. 3. 701 agouti, yellow and white, normal F_3 ♂. A normal animal from the fourth generation of the control; slightly inbred, natural size. Birth weight, 63 grams.)

FIG. 4. 599 black, white and red. F_3 ♂. A degenerate animal from the fourth generation alcoholic lines; no inbreeding; the paternal grandmother had both parents alcoholic and the maternal grandfather had both parents alcoholic. So there were two alcoholic great-grandmothers and two alcoholic great-grandfathers; the other four great-grandparents were normal and one grandmother and one grandfather had no alcoholism in their ancestry. The parents were ♂ (NN) (AA) ♀ (AA) (NN). The animal lived seven days and died in convulsions. The photograph shows the front limbs bent under the body and the animal is unable to raise the head. It weighed only 35 grams at the time of death, having lost 7 grams. While the above normal animal weighed 63 grams, actually a little small, at birth and all normal animals increase in weight rapidly from that time.

litters of one than from the litters of two. Not one deformed animal has resulted from these normal inbred matings and only one individual of the thirty was less than two thirds the average weight. The few normal inbred young here considered are then equally as good as the young from normal non-relatives and necessarily superior to the alcoholic lines. Judging from the results of others, there is little doubt that a more extensive inbreeding might produce deleterious effects.

The last vertical column indicates the effects of inbreeding alcoholic animals and their descendants. This combination shows the poorest quality offspring found in the table. Here again the members of the larger litters are at a disadvantage when compared with those born in the small litters. The average number of young in a litter is 1.62, somewhat smaller than the litters produced by mating alcoholic non-relatives. Thirty-eight litters contained a single individual each, the same number of litters contained two individuals, while only seven litters consisted of three young, and these were the largest litters produced. The inbred alcoholic animals, therefore, have a tendency to produce a large proportion of small litters and this tendency aids in strengthening their offspring.

Of the 135 young resulting from these matings, only 36.29 per cent. of them survived; this is the poorest life record shown by any combination. Of those born only one in a litter, however, 76.31 per cent. survived, which is a record equal to the average of the control. Therefore, even in this very bad combination, alcoholic inbreeding, when only one young is produced at a litter by an animal ordinarily capable of producing two or more, this one young is so well nourished and accommodated that it is somatically vigorous. Yet on breeding such individuals it almost always happens that very inferior offspring result. The germ cells, at any rate, may possibly be stronger than those in the weaker individuals which occurred in litters of two or three. Only 26.31 per cent. of the animals born in litters of two were capable of sur-



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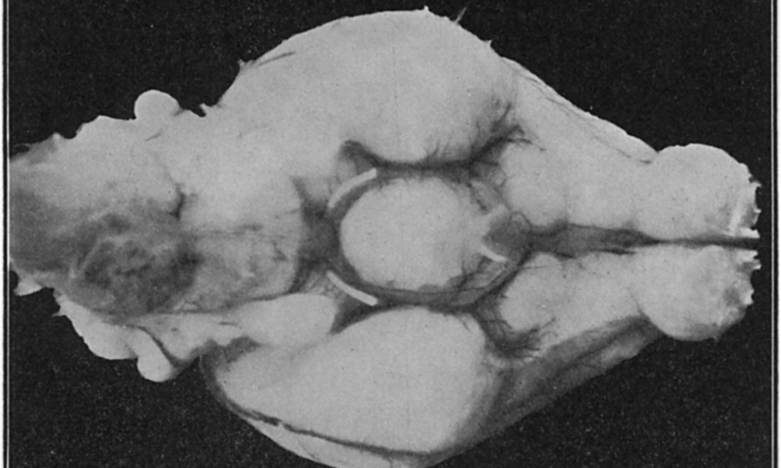

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FIG. 5. Ventral view of a normal guinea-pig brain killed three days after birth. The optic nerves, optic chiasma and optic tracts passing along the tuber cinereum are distinctly seen.

FIG. 6. Ventral view of the brain of an anophthalmic monster from alcoholic great-grandfathers. There are no optic nerves, chiasma or tracts; the only indication of optic parts being two small membranous processes about in the position of the optic chiasma.

viving. The mortality here happens to be about three times higher than among the single-litter individuals. And further, not one of the 21 specimens born in litters of three lived. Among the offspring from the alcoholic inbred lines, judging from the numbers now available, the difference between the vitality of individuals born in litters of one and those born in larger-size litters is most striking.

The space below is the reverse of the one just considered and gives the percentage of young dying in the different litters. Only 23.68 per cent. died from litters of one individual, while 73.68 per cent. died in the litters of two individuals, and every one, 100 per cent., of the animals born in litters of three died within three months and usually within a few days.

The proportion of deformed animals occurring in the different-size litters again emphasizes the same differences in quality. All together 14.81 per cent. of the 135 individuals were grossly deformed; this is the highest percentage of deformed animals occurring in the several combinations represented in the table.

Of those animals born one in a litter only 5.26 per cent. were deformed; of those born two in a litter 18.42 per cent., or more than three times as many, were deformed, and of those specimens born in litters of three 19.04 per cent., or about one in five of them, were grossly deformed.

The proportion of deformities, therefore, conforms to the mortality records, being very much higher in the larger litters, and not unusually high among the individuals born one in a litter as compared with the average percentage of deformities from alcoholic non-relatives. Therefore, the bodily quality of the offspring is not materially worse from alcoholic inbred animals than from matings of alcoholic non-relatives, provided only one individual is born in the litter. But when more than one individual occurs in the litter, the alcoholic inbred combination is the most disastrous for the vitality and form of the offspring of all the combinations considered.

The last space shows that 3.7 per cent. of these offspring were less than two thirds the normal size. This again compares unfavorably with the other combinations, and here also the individuals born one in a litter show a superiority over those born in litters of two.

From a consideration of this table it may be concluded that the vigor of a guinea pig varies inversely with the size of the litter in which the animal is produced, and this is equally true whether the animal is born from normal or alcoholic parentage. However, the differences between the mortality of animals born in litters of one, two or three from normal parentage are not nearly so great as comparable differences between the members of the small and large litters from alcoholic lineage. For example, the difference in mortality between normal animals in litters of one or two is about 1 per cent., or scarcely any; between these and the mortality of specimens born three in a litter there is a difference in mortality record of about 24 per cent., to the discredit of the larger litters.

The comparable differences in the alcoholic lines is ever so much greater. There is almost 14 per cent. higher mortality among individuals from litters of two than from litters of one, and actually about 43 per cent. higher mortality among animals from litters of three than from litters of one. The difference between the mortality percentages in the litters of one and the litters of two from alcoholic inbred animals is 50 per cent. In other words, the mortality is three times as high among individuals from litters of two as from litters of one in inbred alcoholics, while the normal individuals born in litters of two are equally as good as those in litters of one. The parents from the injured alcoholic lines are incapable of producing large litters of strong individuals. The subnormal fetus fares pretty well alone in the uterus but is put at a great disadvantage by having to divide its uterine nourishment with brothers and sisters.

Another almost equally plausible explanation of this striking difference in quality and vitality among the members of small and large litters might be given. It may be supposed that the growth capacity of the eggs maturing in the ovaries of normal and subnormal individuals depends somewhat upon the number of eggs maturing at any one time, or ovulation period. A normal animal may be capable of developing two entirely good eggs at an ovulation, or possibly three, whereas a weakened, less vigorous individual has ovaries incapable of producing more than one well-nourished or well-developed egg at any one time. Of course, it is understood that the small size of a mammalian egg would make it seem as though it required very little stored food from the ovary, yet that little must be of an extremely fine quality, since so much of the energy of early development is derived from the materials stored within the egg.

One point which might be interpreted to favor such an explanation is the fact that the small, weak young contained in the large litters do not recover and make their shortage good after birth, as might be expected if their inferior condition was simply due to a lack of nourishment available in the overcrowded uterine environment in which their late stages of development were passed. Lack of intra-ovarian nutrition would certainly produce a more lasting effect, since it occurs at an earlier stage than lack of uterine nutrition, though of course we do not pretend to deny that poor uterine nutrition would also leave its persisting mark.

When only one young was produced in a litter the average growth rate of such individuals during the first month after birth was 85.09 grams. Such specimens were not only largest at birth, but they grew fastest after birth. Animals born in litters of two increased 68.46 grams during the first month after birth, while those born three in a litter gained only an average of 63.6 grams during the same period. In other words, the last group only gained 75 per cent. of the amount gained by similar specimens which were fortunate enough to be developed alone in the ovary and in the uterus.

A second conclusion indicated by Table II is that inbreeding the defective alcoholic stock produces a quality of offspring decidedly inferior to that produced by the alcoholic lines when not inbred. This involves the internal factors of the germ cells. When a modified germ cell is united with a related one probably modified in a closely similar manner, a summation of the modification produces a more decidedly modified individual than would result from the combination of two non-related germ cells, even though they also be modified. In other words, as is shown in much of the data on heredity in higher animals, relatives probably respond to the treatment more nearly in the same way than do non-relatives, and there fore inbred defectives produce the most disastrous results obtainable.

THE RELATIVE CONDITIONS OF THE MALE AND FEMALE DESCENDANTS FROM PATERNAL AND FROM MATERNAL ALCOHOLIZED ANCESTORS

We may now consider the possibility of analyzing the relative influences of various alcoholized ancestors on their offspring of different sex and the descendants of such offspring. The problems may be stated thus: are the offspring from alcoholized males more or less degenerate or modified than those from alcoholized females, and is there a difference in the degree of degeneracy between the male and female offspring? Are the descendants from alcoholic grandparents on the father's side more or less defective than the descendants from alcoholic grandparents on the mother's side, and do alcoholized grandfathers and grandmothers show an equally strong tendency to stamp their grandchildren? Do the grandsons and granddaughters show relatively different conditions, depending upon whether they are descended from alcoholized grandfathers on the father's or the mother's side or from alcoholized grandmothers on the paternal or the maternal side?

Table III, which excludes all inbred animals, is a sum-

TABLE III

THE RELATIVE DEGENERATIVE INFLUENCE OF MALE AND FEMALE ALCOHOLIZED ANCESTORS ON THEIR MALE AND FEMALE DESCENDANTS. (ALL INBRED ANIMALS ARE EXCLUDED)

	Males with	Females with	Young of Unknown Sex with	Males with	Females with	Young of Unknown Sex with	Males with	Females with	Young of Unknown Sex with	Males with	Females with	Young of Unknown Sex with	Males with	Females with	Young of Unknown Sex with	Males with	Females with	Young of Unknown Sex with
	Alcoholized Father			Alcoholized Mother			Alcoholized Grandfather on the Father's Side			Alcoholized Grandfather on the Mother's Side			Alcoholized Grandmother on the Father's Side			Alcoholized Grandmother on the Mother's Side		
Total number..	44	43	70	37	23	38	36	38	26	34	32	48	37	33	36	23	18	25
Lived over 3 months.....	37 84.1%	33 76.74%	0	34 91.89%	22 95.65%	0	26 72.22%	23 60.52%	0	23 67.64%	19 59.37%	0	25 67.56%	23 69.69%	0	18 78.25%	14 77.77%	0
	44.58%			57.14%			49%			36.84%			45.28%			48.48%		
Died within 3 months......	7 15.9%	10 23.25%	70 100%	3 8.1%	1 4.34%	38 100%	10 27.77%	15 39.47%	26 100%	11 32.35%	13 40.62%	48 100%	12 32.43%	10 30.30%	36 100%	5 21.74%	4 22.22%	25 100%
	55.41%			42.85%			51.0%			63.15%			54.71%			51.51%		
Deformed.....	1 2.27%	2 4.65%	3 4.28%	0	0	0	3 8.33%	4 10.52%	0	1 2.64%	4 12.5%	7 14.58%	2 5.40%	3 9.03%	7 16.66%	2 8.69%	0	0
	3.82%			0			7.0%			10.52%			10.37%			2.77%		

marized analysis of these questions. The male and female descendants from six different lines are tabulated. The table is not perfectly pure, but merely represents a mass result, since, for instance, in giving the young from alcoholized fathers some of these young had also alcoholized grandparents, etc. The same is true of the other lines. But the large majority of the figures are from unmixed matings, so that these mass results do have some real significance.

In the first vertical section is given the records of offspring from alcoholized fathers. Forty-four males, 43 females and 70 young of unknown sex are considered. Of the males 84 per cent. lived, and 76.7 per cent. of the females lived. These numbers are very high, since in the early part of the experiment only those young which survived were catalogued for sex. Therefore, all of the 70 young of unknown sex were animals which died at birth or soon after, and as the table shows more than half of the animals from alcoholized fathers died soon after birth.

The mortality among the male offspring from alcoholized fathers was 15.9 per cent., while among the female offspring it was considerably higher, being 23.25 per cent. The same difference in quality between the sexes is illustrated by the percentage of gross deformities. Only 2.27 per cent. of the males were deformed, while twice as great a proportion, or 4.65 per cent., of the female offspring from treated fathers were deformed. In all 3.82 per cent. of the offspring from alcoholized males were deformed and the female offspring were inferior in quality to the male.

The next section of the table presents similar data for the offspring from alcoholized mothers. There were 37 male, 23 female and 38 offspring of unknown sex. Again, the offspring in which the sex was ascertained during part of the experiment were only those that survived, therefore, their mortality record is very good, while all the animals of unknown sex were individuals that died shortly after birth. Yet the records of the males and females are based on exactly the same kind of data and are to be fully compared. Eight and one tenth per cent. of the males died, while only 4.34 per cent., proportionately about half as many, females died. Not one grossly deformed animal was found among the offspring of alcoholized females.

Thus from the mortality records the sons of alcoholized mothers appear more affected than their daughters. And taken as a whole the records of the alcoholized mothers are superior in quality to those of the alcoholized fathers, thus indicating that the male germ cells are more injured by the treatment than the female germ cells.

The third section shows the records of the male and female descendants from alcoholized grandfathers on the father's side. Here the mortality record of the males is much better than that of the females; 27.77 per cent. of the males died soon after birth, and 39.47 per cent., a very much higher proportion of the females, died.

The mortality of these animals from alcoholic grandparents seems much greater than that of animals from treated parents; this is due, however, to the fact that the sex of many more of these that died at birth was ascertained as they occurred later in the experiment when this point was being watched. The totals are the only figures in the horizontal mortality columns that are to be compared. The total mortality of descendants from alcoholic grandfathers on the father's side was 51 per cent., which is higher than the mortality of the offspring from alcoholized mothers, 42.85 per cent., but lower than the mortality of offspring from alcoholized fathers, which reached 55.41 per cent.

Among the ascertained male descendants from an alcoholized paternal grandfather 8.33 per cent. showed gross deformities, while 10.52 per cent. of the descendants ascertained to be female were deformed. Considering all the animals in this group, 7 per cent. were deformed, which is almost twice as great a proportion as occurred among the offspring of alcoholized fathers. *The deform-*

ities in the F_2 generation are more frequent than in the F_1.

The fourth section shows the influence on the grandchildren of an alcoholized grandfather on the mother's side. This is the most injurious combination shown. Only 36.84 per cent. of the offspring survive. Of the male descendants of an alcoholized maternal grandfather 32.35 per cent. died soon after birth, while proportionally many more, or 40.62 per cent., of the female descendants died. In all a total of 63.15 per cent. of the descendants from alcoholized maternal grandfathers died, which is the highest mortality record obtained.

Among the grandchildren of alcoholized maternal grandfathers 10.52 per cent. were deformed, a very high proportion. But of the grandsons only 2.64 per cent. were deformed, while almost five times as many, or 12.5 per cent., of the granddaughters were grossly deformed. Thus *the females of the F_2 generation from a treated maternal grandfather are poorer when considered from the standpoint of mortality record and bodily structure than the male F_2's from the same source.*

The fifth line to be considered is that of an alcoholized grandmother on the father's side. The result of this treatment as shown by the grandchildren is very bad, but not quite so bad as from the alcoholized maternal grandfather just discussed.

From alcoholized paternal grandmothers the conditions of 37 grandsons and 33 granddaughters are to be compared. About the same survival record is shown by both sexes: 67.56 per cent. of the male grandchildren lived and 69.69 per cent. of the females lived. Of all the descendants from this combination, including those in which the sex was not determined, only 45.28 per cent. survived, giving a mortality record of 54.71 per cent., considerably better, by almost 10 per cent., than that of animals from an alcoholized maternal grandfather in the preceding section.

A large proportion of the animals from alcoholized paternal grandmothers were deformed, 10.37 per cent. However, only 5.4 per cent. of the grandsons were deformed, while many more, 9.03 per cent., of the granddaughters were deformed and among the young of undetermined sex 16.66 per cent. were deformed.

In the last section the records of descendants from alcoholized grandmothers on the mother's side are given. There were 23 males, 18 females, and 25 young which died with their sex unascertained. Forty-eight and forty-eight hundredths per cent. of the animals lived. The mortality among the males was 21.74 per cent., about the same as that of the females which was 22.22 per cent. The total mortality being 51.51 per cent. From this combination there occurred a low percentage of deformities, confined entirely to the grandsons. *So that 8.69 per cent. of the grandsons from alcoholized maternal grandmothers were deformed, while none of the granddaughters showed any gross structural abnormalities.*

TABLE IV

MORTALITY DURING THE FIRST THREE MONTHS OF THE DESCENDANTS OF KNOWN SEX FROM ALCOHOLIC ANIMALS (NOT INBRED)

Treated with Alcohol	Males			Females			All Together		
	Total Number	Died Early	Mortality	Total Number	Died Early	Mortality	Total Number	Died Early	Mortality
Father	44	7	15.90%	43	10	23.25%	87	17	*19.54%*
Mother	37	3	8.10%	23	1	4.34%	60	4	*6.66%*
Grandfather on father's side	36	10	27.77%	38	15	39.47%	74	25	*33.78%*
Grandmother on father's side	37	12	32.43%	33	10	30.30%	70	22	*31.42%*
Grandfather on mother's side	34	11	32.35%	32	13	40.62%	66	24	*36.36%*
Grandmother on mother's side	23	5	21.74%	18	4	22.22%	41	9	*21.95%*

Table IV presents in a more concise manner certain of the figures considered in the foregoing Table III. Only the mortality records of the male and female descendants from different sources and the total mortality of the several groups is shown by the table and thus a ready comparison of the conditions may be made. Among the offspring from alcoholic fathers 15.9 per cent. of the males died and 23.25 per cent. of the females. *The fe-*

male are more injured than the male offspring of treated fathers. The next horizontal line shows that *the offspring from treated mothers are far better than from treated fathers,* having a much lower mortality. *The male germ cell is more affected by the alcohol than the ovum, therefore treated fathers produce poorer offspring than treated mothers.*

The heterogeneous female descendants from an alcoholized paternal grandfather are more affected than the male, 39.47 per cent. mortality to 27.77 per cent.

The male and female descendants from an alcoholized paternal grandmother show about equal conditions, 32.43 per cent. male mortality to 30.3 per cent. female mortality.

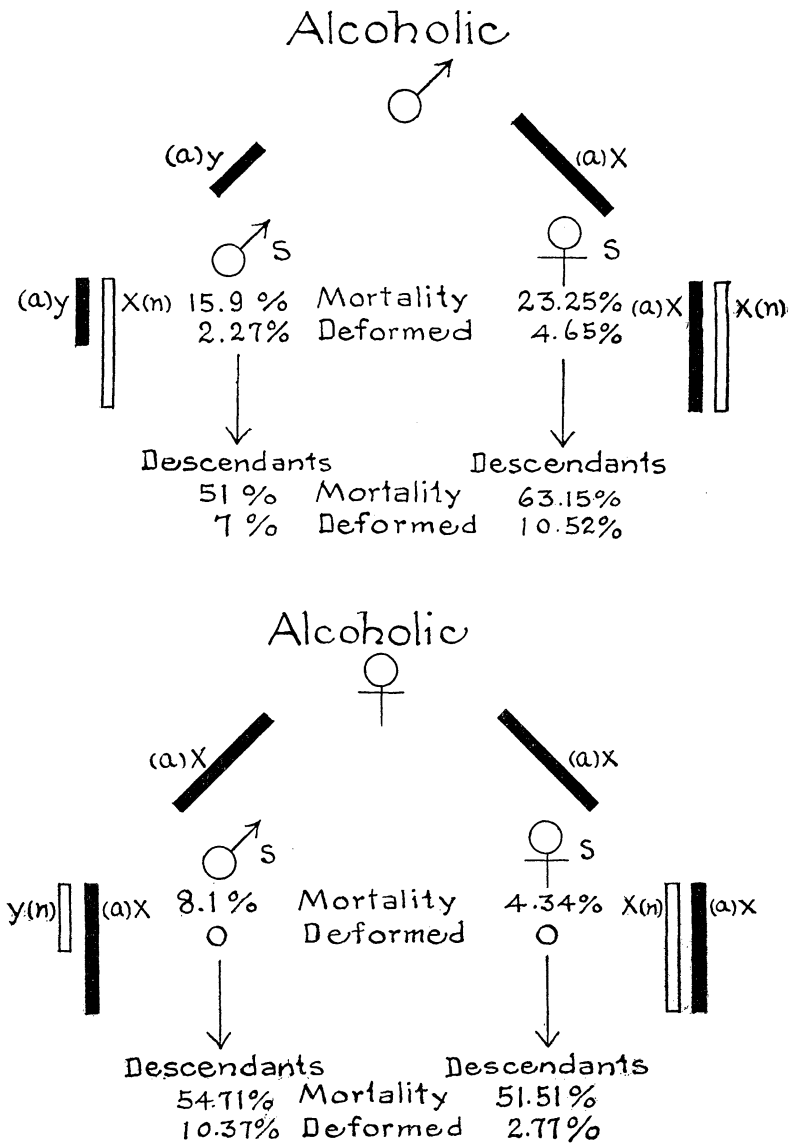
The heterogeneous female descendants are inferior to similar male descendants from an alcoholized maternal grandfather, 40.72 per cent. female mortality to 32.25 per cent. male mortality.

The male and female descendants are about equally strong from an alcoholized maternal grandmother, 21.74 per cent. male mortality to 22.22 per cent. female mortality.

Although explanations of the above differences between the ways in which the male and female guinea pigs are affected by the treatment, as well as explanations of the different records of the grandsons and granddaughters from alcoholization of different ones of the four grandparents, are difficult to give at the present stage of the experiment, a tentative explanation based on the composition of the chromosomal complex is certainly suggested.

GENERAL CONSIDERATIONS

In the case of the male guinea pig, according to the studies of Miss Stevens ('11), two kinds of spermatozoa are produced. The one has a large X chromosome, the female-producing spermatozoon, and the other contains a corresponding small Y chromosome, which from homology with other forms we may consider to be the male-producing. The two classes of spermatids are different



The diagram intended to show the difference in quality between the male and female offspring of alcoholized males and females, and indicating a possible explanation of these differences. The upper part of the diagram represents the heteromorphic chromosomes X and Y of the male passing to the male and female offspring. The larger injured X chromosome gives a larger proportion of deformities and a higher mortality to the females and their descendants. The smaller injured y chromosome gives to the males and their descendants a proportionately smaller amount of deformities and a lower mortality record.

The lower part of the diagram shows equal amounts of injured chromatin passing from the treated mother to her male and female offspring, the black X chromosomes. But these equal amounts of modified chromatin are combined with unequal amounts of normal chromatin from the heteromorphic spermatozoa, the unequal white X and Y chromosomes. The male offspring, therefore, have in their chromosomal constitution proportionally more modified and less normal chromatin than the female offspring which have equal amounts of normal and alcoholic. And the male offspring and their descendants are actually found to show a higher mortality and a greater proportion of deformities than the female offspring and their descendants.

morphologically and we may expect them to differ in their susceptibilities to the alcoholic treatment. One class may be more affected than the other. This might be due simply to the reason that one class of spermatozoa actually according to mass has more chromatin to be acted upon than the other. And this difference in mass of affected chromatin might be sufficient to give a difference in quality between the individuals arising from the two classes of spermatozoa.

At any rate, as the accompanying diagram indicates, there is a decided difference between the records of the male and female offspring from treated guinea pigs. The upper half of the accompanying diagram shows that the mortality is higher and the gross deformities more frequent among the female offspring sired by alcoholized male guinea pigs than among the male offspring. This difference we may venture to suppose is due to the fact that the female offspring actually receive more modified or injured chromatin from the alcoholic father than do the sons. The diagram is an attempt to represent this larger mass of injured chromatin, the large black X chromosome passing to the daughters, while the smaller black Y chromosome is received by the sons.

Another possible explanation might be that the two heteromorphic sex chromosomes, the X and Y, respond differently to the influence of the alcoholic treatment, the X being the more affected. Such an opinion has some basis, since these chromosomes in the later development of the two sexes seem to carry such a number of contrasting qualities according to the splendid evidence presented by Morgan and his associates. One may be permitted to assume on probability, at any rate, that the X and Y chromosomes are qualitatively different in their finer chemical constitutions, and this qualitative difference would necessitate a different response to the chemical treatment on the part of each of the two chromosomes.

There is also important evidence from the parthenogenetic groups, as, for example, the Phylloxerans and

Aphids (Morgan, '09), which might lead one to believe that the two classes of spermatids or finally spermatozoa are never quite equally active or vigorous. This difference may vary from apparent equality in most higher animals to cases such as the parthenogenetic Phylloxerans and Aphids, in which one class of spermatids are actually degenerate and non-functional.

In this connection an experiment performed with a quite different problem in view by Cole and Davis ('14) with alcoholized rabbits is suggestive. They found that when two male rabbits were mated with a female superfetation occurred in most cases so that part of the resulting litter of young were sired by one male and part by the other. The two males differed in their ability, so that one more often sired the majority of young of a given litter and in the total number of competition matings sired the greater number of young. When this male with the fertilizing advantage was treated for a short period of time, a month or more, with fumes of alcohol he was then affected in such a way that when mated in competition with the same male he normally had beaten he now failed to sire any young. Yet if mated singly or alone with a female he still had the power to beget offspring. The alcohol treatment had in some way lowered the power of his spermatozoa to fertilize an egg. Thus these spermatozoa could no longer fertilize an egg in the presence of the spermatozoa from a male which was originally less potent than they.

All of these data indicate differences in the behavior and reactions of the individual germ cells, and such differences probably account for the discrepancy existing between the conditions of the male and female offspring from an alcoholized father. Since this point has only recently been discovered in the experiments, we now have very few definite matings to test its meaning by back crosses with the normal. But a large number of heterogeneous matings have been made during the last few years and their gross results serve to verify the fact that the difference in quality between male and female offspring is actual, although such matings furnish no definite analysis of the conditions.

In the first place, the upper half of the diagram shows that the mortality is higher and the defects more frequent among the female offspring of treated males than among their sons. The products of the heterogeneous matings in which these male and female offspring have taken part go to indicate that the first apparent difference in their records was a real difference. The mortality record of the mass descendants from the sons of alcoholized fathers is about 20 per cent. better than the mortality record from the descendants of the daughters of alcoholic fathers. And the proportion of deformities is 50 per cent. higher among the descendants of the daughters than among the descendants of the sons. These conditions of the descendants prove that the female offspring from the alcoholized males are actually worse than the male offspring in the following respects: their mortality record, the frequency of deformities, and the quality of young to which they give rise. The only plausible way to account for the origin of this difference is to assume that the female-producing spermatozoa were more modified by the treatment than the male-producing spermatozoa. Whether such an increased modification is due to the presence of a greater mass of chromatin to be injured in the one case than in the other or to a difference in response on the part of the two heteromorphic sex chromosomes it is impossible to state. The difference, however, is a fact!

The lower half of the diagram illustrates the different qualities of the male and female offspring from alcoholized mothers. Here each sex of the offspring in accordance with prevalent cytological views receives an equal amount of chromatin from the treated mother. And, moreover, as far as the treated mother is concerned similar chromosomal complexes are conveyed to both sexes of the offspring. The two classes of young should, therefore, show similar conditions, but such is not the case.

The mortality of the male offspring is higher than that of the female. This condition may probably be explained on the same principles we have employed above. The two sexes receive equal amounts of injured chromatin from their alcoholized mother, but this injured chromatin in the case of the female individuals is mixed with a larger amount of normal chromatin from the father than is the case with the male. The female combination of equal amounts of good and bad chromatin gives rise to a better product than the male combination of a larger amount of modified chromatin with a smaller amount of good. Therefore the records of the male offspring are inferior to those of the female offspring.

The female combination, ovum and spermatozoon with equal amounts of chromatin, good and bad, is proportionately less injured than the male combination, ovum with a larger amount of bad and spermatozoon with a smaller amount of normal chromatin. The diagram represents the black X chromosomes equal in size passing to the daughters and the sons to be combined with the large white normal X in the case of the daughters and with the small white normal Y in the case of the sons.

Again the descendants from heterogeneous matings of these males and females prove that there is an actual difference in quality. The descendants from the sons of alcoholic mothers show a slightly higher mortality and a much greater proportion of deformities than are found among the descendants of their daughters.

We believe that these results actually show a difference in response to the treatment on the part of the male- and female-producing spermatozoa. Such a difference logically follows the cytological differences in structure which Wilson and others have so clearly demonstrated during the past ten years. If this structural difference is of any significance, as it surely must be, then such physiological differences in behavior as are indicated in our results should sooner or later be found.

On such a basis as this the sex ratio in different classes of animals may possibly be explained. A species such as man, which constantly seems to produce more males than females, may be said to form more active or vigorous male-producing spermatozoa. In the competition to fertilize the egg such spermatozoa win an advantage and in the sum total more males than females arise, the ratio depending upon the extent of the advantage the one class of spermatozoa has over the other.

We now have under way a number of matings which are designed to test these propositions in an analytical fashion. One of us (Papanicolaou, '15) is in possession of data giving reason to believe that a second explanation may be offered to account for the different conditions presented by the male and female offspring produced by alcoholized females. Such an explanation is based on the supposition that the female guinea pig as well as the male has a share in the determination of the sex ratio and may produce two kinds of ova. Such an explanation in its final analysis is extremely complex and unnecessary in the present discussion, though it will be presented in a future consideration of the regulation of the sex ratio in these animals.

Admitting, as is suggested above, that the two groups of spermatozoa differ in their response and resistance to the treatment, we may also admit that there are other normal differences in their vitality and behavior. These normal differences must also vary within certain limits. In one group of animals the female-producing spermatozoa may be more active and possess a higher degree of fertilizing power than the male-producing spermatozoa. Such a group would show a sex ratio below one hundred, there being more females than males produced. In other species of animals with a sex ratio of more than 100 the reverse condition obtains; the male-producing spermatozoa possess on an average a higher fertilizing power than the female-producing. But the advantage of the male-producing sperm may be slight and no doubt many individual males tend to form female-producing sperm with a higher fertilizing power than the male-producing. Such individuals will more frequently beget female offspring. Slight differences in the physiological behavior of the two classes of spermatozoa would account for the sex ratios in all animals, and finally, as Morgan has shown, the extreme difference between the qualities of the two classes of spermatozoa leads to the degeneration of one entire class and the necessary production of only one sex from the fertilized eggs of these species. Such species must also be parthenogenetic in order to produce individuals of the other sex.

This discovery by Morgan suggests, as Wilson ('11) brings out in his review of the sex chromosome question, a plausible explanation of the sex ratios in different classes of animals. And we believe the evidence presented above lends further support to such an interpretation.

A rather old popular idea in attempting to explain the sex riddle may have some ground of fact from the standpoint of the variations in the differences of fertilizing power of the two classes of spermatozoa. It has often been claimed that one testis is male-producing and the other female-producing. Every one knows that this is untrue. Yet one testis may have a tendency to produce spermatozoa of the female class with a higher fertilizing power than the male sperm of this testis, and the other testis might have an opposite tendency, since the conditions of behavior often differ in two organs of a bilateral pair. An animal which has produced a large proportion of male offspring may after semi-castration produce almost all female offspring. A possible explanation for such an occurrence would be that the removed testis had produced more vigorous male sperm than female and the spermatozoa of this testis possessed the higher fertilizing power, while the remaining testis tended to produce more potent female sperm. On removing the one testis the other came into supremacy. In the same imaginary case, if the opposite testis had been removed, there would have been no change in the tendency to produce offspring of a certain sex, since the remaining testis originally possessed an advantage.

Finally, then, from the above experiments there is no question that the material basis of the hereditary qualities has been injured, since alcoholized males have transmitted the injury to four generations during a period of almost five years. In other words, as stated above, chromatin injured five years ago is now living in the great-grandchildren of the individuals in which it was injured.

Bardeen with the X-ray and Oscar Hertwig with radium have induced similar injuries by directly treating the spermatozoa, but these cells were so greatly injured that only the immediate effect upon the developing embryo was shown. The present experiments, however, demonstrate the passage or transmission of the injured chromatin from generation to generation during a period of years. *The behavior of the carriers of heredity becomes pathological just as any other organ with a normal function may behave in an abnormal or pathological manner.*

Mammals are particularly adapted to the study of such features of heredity as this, on account of their typical structure and large, easily observed organs. The complexity of their structure and behavior further permit the possibility of slight modifications becoming visible through abnormal conditions of their nervous system, etc. Thus with such material as guinea pigs a few experiments of this kind may furnish certain clues to the processes of behavior of the chromosomes that less plastic and simpler forms might never present in such a manner as would be recognizable.

On the other hand, the small litters and comparatively slow breeding render these higher animals unsuitable for an exhaustive analysis of many of the intricate problems of normal heredity.

SUMMARY AND CONCLUSIONS

In the foregoing pages we have considered the results of an experiment now in progress for more than five years which analyzes to some extent the influence on the offspring of alcoholizing either one or both parents and the manner of hereditary transmission of the induced effects to subsequent generations.

The experiments have demonstrated on two different stocks of normal guinea pigs that the parental germ cells may be so modified by chemical treatments that they are rendered incapable of giving rise to a perfectly normal offspring. This incapacity is probably due to modifications of the chromatin or carriers of the hereditary qualities within the germ cells, since the great-grandchildren, the F_3 generation, from the treated animals are usually more decidedly affected and injured than the immediate offspring (F_1) of the alcoholized animals.

This then becomes a study of the behavior of diseased or pathological chromatin in heredity. Chromatin rendered pathological more than four years ago is still living and has now been passed on to the F_3 generation from the alcoholized great-grandparents. The F_3 animals are almost without exception incapable of reproduction and are in many ways subnormal and degenerate.

Studies of abnormal heredity may possibly furnish a means of analyzing the normal methods of action by which the minute carriers of hereditary qualities contained within the fertilized egg are capable of causing complex developmental and structural changes to reoccur from generation to generation in so wonderfully consistent a manner. Just as the knowledge furnished by studies of experimentally modified embryonic development has supplied valuable data towards a clearer understanding of the normal processes and changes which occur in the developing embryo.

The treatment of adult guinea pigs by an inhalation method with daily doses of alcohol through several years produces little if any noticeable effect upon the organs and tissues of the animal's body. The direct action of alcohol fumes tends to injure the respiratory mucosa and to render the cornea of the eye dull or opaque. These changes, however, do not inconvenience the animals in any perceptible way, and they remain strong and hardy and live as long and actively as the untreated guinea pigs. In spite of their healthy appearance the injurious influence of the alcohol inhalation is very decidedly shown by the quality of offspring to which the treated animals give rise. And the descendants of these offspring are even worse than the F_1 generation when compared with the different generations of control animals produced under identical cage and food conditions.

The males seem to be more injured by the treatment than the females, taking as an index of injury the quality of their offspring and descendants. Stating it differently, the spermatocytes or spermatozoa are more sensitive to the changed chemical condition of the tissues than are the female germ cells.

There is a larger proportion of degenerate, paralytic and grossly deformed individuals descended from the alcoholized males than from the alcoholized females.

The records of 682 offspring produced by 571 matings of animals of various types have been tabulated to show the kinds of litters of young produced and their ability to survive. One hundred and sixty-four matings of alcoholized animals, in which either the father, mother, or both were alcoholic, gave 64, or almost 40 per cent., negative results or early abortions, while only 25 per cent. of the control matings failed to give full-term litters. Of the 100 full-term litters from alcoholic parents 18 per cent. contained stillborn young, and only 50 per cent. of all the matings resulted in living litters. Forty-six per cent. of the individuals in the litters of living young died very soon after birth. In contrast to this record 73 per cent. of the 90 control matings gave living litters and 84 per cent. of the young in these litters survived as normal, healthy animals.

The mating records of the descendants of the alcoholized guinea pigs, although they themselves were not treated with alcohol, compare in some respects even more unfavorably with the control records than does the above data from the directly alcoholized animals.

Of 194 matings of F_1 animals in various combinations 55 have resulted in negative results or early abortions, 18 stillborn litters of 41 young occurred, and 17 per cent. of these stillborn young were deformed. One hundred and twenty-one living litters contained 199 young, but 94 of these died within a few days and almost 15 per cent. of them were deformed, while 105 survived and 7 of these showed eye deformities. Among 126 full-term control young of the same stock not one has been deformed.

The records of the matings of F_2 animals are still worse, higher mortality and more pronounced deformities, while the few F_3 individuals which have survived are generally weak and in many instances appear to be quite sterile even though paired with vigorous, prolific, normal mates.

The structural defects shown by the descendants of alcoholized animals seem to be confined chiefly to the central nervous system and special sense organs. Many of the young animals show gross tremors, paralysis agitans; the hind legs, fore legs or both legs of one side may be paralyzed (Plates I and II). Eye defects are very common, such as opaque cornea, opaque lens, various degrees of monophthalmicum asymmetricum, and finally several cases of complete anophthalmia have occurred, the entire eyeballs, optic nerves and optic chiasma being absent (Figs. 1 to 3 and Plate III).

The quality of individuals from the same parentage varies inversely with the size of the litters in which they are produced. Animals born one in a litter are rather strong, even though derived from very bad alcoholic lines. This difference between the members of small and large litters is also shown by the normal animals, but the difference in quality between members of large and small litters is ever so much greater in the alcoholic lines. There is also some tendency on the part of the alcoholic animals to produce a greater proportion of small litters and this aids somewhat towards the perpetuation of their lines.

Inbreeding tends to emphasize the alcoholic effects. This is probably due to related animals responding to the treatment in closely similar ways on account of the similarity of their constitutions. Inbreeding, as such, may be harmful. But inbreeding added to the alcohol effects produces a much worse condition in the offspring than either inbreeding or alcoholism alone could do.

The data from alcoholized male lines indicate that the *female offspring from alcoholic males are less viable and more frequently deformed than the male offspring. And heterogeneous matings of such male and female offspring further emphasize the same inferiority on the part of the female offspring from treated males.* This is a very significant fact.

The fact that the offspring of one sex differ in quality from those of the opposite sex, and that the female offspring of an alcoholic male are inferior to his male offspring suggests at once a difference between the germ cells concerned in the production of the male and female young. Miss Stevens showed that the spermatocytes of the male guinea pig contained a heteromorphic pair of chromosomes and half of the spermatozoa would be expected to receive one member, the X chromosome, of the heteromorphic pair and one half of the spermatozoa the other member, the Y chromosome, of the heteromorphic pair. We now have two possibilities in explanation of the above facts. In the first place, it may be assumed that the alcohol acts similarly on all of the chromatin to injure it. Thus a mass action would cause the spermatozoa carrying the larger member of the heteromorphic pair to deliver more injured chromatin and the other spermatozoa with a less total amount of injured chromatin would deliver less when they fertilize eggs containing equal amounts of normal chromatin. The fertilized egg giving rise to the female, therefore, contains a greater proportional amount of alcoholic chromatin to normal chromatin than does the egg giving rise to the male. And so the female product is actually more injured than the male.

A second possible explanation of these conditions may be that the X and Y chromosomes themselves respond differently to the treatment, the X being the more sensitive of the two. But in either case the two classes of spermatozoa certainly seem to respond differently to the treatment and this shows a physiological difference in behavior to correspond with the well-known morphological differences so often found between the two groups of spermatids of many animal species.

The data from alcoholic female lines indicates that *the male offspring from alcoholic females are inferior in quality to the female offspring. And heterogeneous matings of such male and female offspring further prove the inferiority on the part of the male offspring from treated mothers.* This is also significant. How can it be put in accord with the above chromosomal explanations for the difference in quality between the female and male young of alcoholized fathers?

If we admit that all of the eggs arising from an alcoholized female guinea pig are homomorphic and contain groups of chromosomes equal in mass, it follows that her male and female offspring receive the same amount of injured chromatin and should be affected by such chromatin to equal degrees. But this is only part of the case, the injured female chromatin is combined with normal chromatin from the normal father when the eggs are fertilized and here the difference arises. The female offspring receives from the normal father a larger amount of normal chromatin than do the male offspring. So that the female arises from an egg in which equal amounts of good and injured chromatin are present, while the male offspring arises from an egg in which a larger amount of injured chromatin is united with a smaller amount of normal. Therefore, proportionally, the male offspring from treated mothers have more injured chromatin in their entire bodily make up than do the female offspring, and are comparatively in a more abnormal condition.

Another explanation of these differences between the male and female offspring of alcoholized females could be based on the possibility of the female being heterozygous for sex. This involves a very complex discussion, but one for which there is some ground on the basis of the regulation of the sex ratio in these animals.

Finally, then, the experiments show the hereditary transmission through several generations of conditions resulting from an artificially induced change in the germ cells of one generation. And they furnish data of importance bearing upon the pathological behavior of the carriers of heredity as well as the differences in behavior between the two types of germ cells produced by an animal carrying heteromorphic chromosomes.

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